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PATENT SPECIFICATION

745,900



Date of Application and filing Complete Specification: June 24, 1952.

No. 15864/52.

Application made in United States of America on Oct. 1, 1951.

Application made in United States of America on Oct. 1, 1951.

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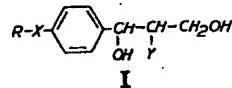
COMPLETE SPECIFICATION

Acylaminodiols and method for preparing same

We, STERLING DRUG INC., a corporation organised under the laws of the State of Delaware, United States of America, of 1450 Broadway, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new chemical compounds and the preparation thereof, said compounds being useful for therapeutic purposes and as intermediates for the production of other chemical compounds.

More particularly, this invention relates to new compounds having the formula

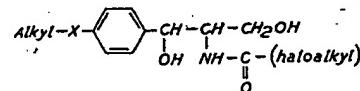


with the threo configuration where R is a hydrocarbon radical having 1—7 carbon atoms, Y is an aliphatic carboxylic acylamino radical, and X is S or SO₂. The hydrocarbon radical R includes aliphatic, cycloaliphatic, aryl, and benzyl radicals having 1—7 carbon atoms, and represents, for example: branched and unbranched alkyl radicals, such as methyl, ethyl, n-propyl, n-butyl, isobutyl, n-heptyl, isooctyl; alkenyl radicals, such as allyl, methallyl; cycloalkyl radicals, such as cyclohexyl, cyclopentyl; benzyl phenyl; and ortho-, meta-, and para-tolyl radicals. The acylamino radicals represented by Y include both saturated and unsaturated aliphatic carboxylic acylamino radicals wherein the aliphatic carboxylic acyl group can be considered as being derived from an aliphatic carboxylic acid. Thus, for example, Y can be alkanoylamino, haloalkanoylamino, nitroalkanoylamino or alkylmercaptoalkanoylamino. We particularly prefer acyclic lower

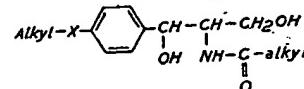
aliphatic carboxylic acylamino radicals containing 1—4 carbon atoms. This preferred group of acyl radicals includes, for example, acetyl, dichloroacetyl, dibromoacetyl, bromoacetyl, beta-chloropropionyl, difluoroacetyl, alpha-chloropropionyl, trichloroacetyl, nitroacetyl, methylmercaptoacetyl, methylsulfonylacetyl, ethylmercaptoacetyl, butyryl, alpha-methylpropionyl, alpha-alpha-dichloropropionyl, iodoacetyl, cyanoacetyl, methoxyacetyl, acryl, and alpha-hydroxypropionyl. 40
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The following groups of compounds embraced by the generic formula hereinabove are illustrative of the products provided by the invention (in each case X in the formulae below is S or SO₂): 50
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2-Haloalkanoylamino - 1-(4-alkylmercapto-phenyl)-1,3-propanediols and 2-Haloalkanoylamino - 1-(4-alkylsulfonylphenyl) - 1,3-propanediols, having the formula 60



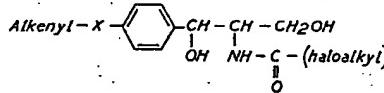
2-Alkanoylamino - 1-(4-alkylmercapto-phenyl)-1,3-propanediols and 2-Haloalkanoylamino - 1-(4-benzylsulfonylphenyl)-1,3-propanediols, having the formula 65



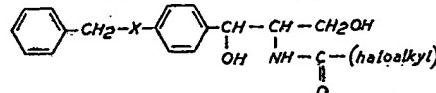
2-Haloalkanoylamino - 1-(4-alkenyl-mercaptophenyl)-1,3-propanediols and 2-Haloalkanoylamino - 1-(4-alkenylsulfonyl- 70

[See 3rd. Ed.]

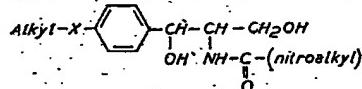
phenyl)-1,3-propanediols, having the formula



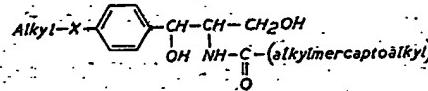
2-Haloalkanoylamino - 1-(4-benzylmercapto-phenyl)-1,3-propanediols and 2-Haloalkanoyl-amino - 1 - (4-benzylsulfonylphenyl) - 1,3-propanediols, having the formula



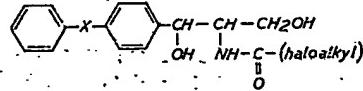
2-Nitroalkanoylamino - 1 - (4-alkylmercapto-phenyl)-1,3-propanediols and 2-Nitroalkanoyl-amino - 1 - (4-alkylsulfonylphenyl)-1,3-propanediols, having the formula



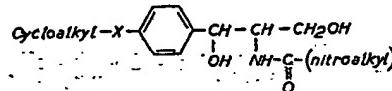
2-Alkylmercaptoalkanoylamino-1 - (4-alkyl-mercaptophenyl) - 1,3-propanediols, and 2-Alkylmercaptoalkanoylamino - 1 - (4 - alkyl-sulfonylphenyl)-1,3-propanediols, having the formula



2-Haloalkanoylamino - 1-(4-phenylmercapto-phenyl)-1,3-propanediols and 2-Haloalkanoyl-amino - 1-(4-phenylsulfonylphenyl) - 1,3-propanediols, having the formula



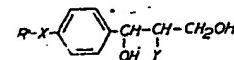
2-Nitroalkanoylamino - 1 - (4 - cycloalkyl-mercaptophenyl) - 1,3 - propanediols and 2-Nitroalkanoylamino - 1 - (4-cycloalkylsulfonylphenyl)-1,3-propanediols, having the formula



In our copending application No. 27387/54

(Serial No. 746,015) there is described and claimed a process for preparing acylamino-phenone compounds which comprises hydroxymethylating a compound of the formula II herein to produce a compound of the formula III herein where X is S.

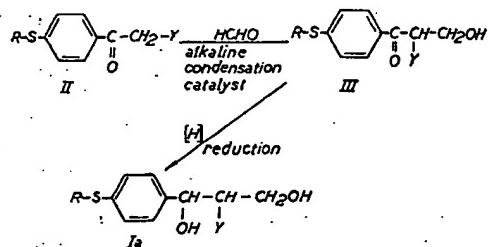
In our copending application No. 27388/54 (Serial No. 746,016) there is described and claimed a process for preparing threo amino diol compounds of the formula I herein in which Y is NH₂ which comprises deacylating a threo compound of the formula



in which Y is an aliphatic carboxylic acylamino radical.

The 2-aliphatic carboxylic acylamino-1-(4-hydrocarbonylmercaptophenyl) - 1,3-propanediols and 2-aliphatic carboxylic acylamino-1-(4 - hydrocarbonylsulfonylphenyl) - 1,3-propanediols of the invention are useful as antibiotic agents, being particularly valuable as antimicrobial agents. For example, they exhibit bactericidal and bacteriostatic action against gram-negative and gram-positive bacteria and rickettsial organisms. The new compounds are also useful as intermediates for the preparation of other valuable organic substances. Thus, for example, they can be hydrolyzed by hot strong mineral acids to produce the corresponding 2-amino-1-(4-hydrocarbonylmercapto-phenyl)-1,3-propanediols and 2-amino-1-(4-hydrocarbonylsulfonylphenyl) - 1,3 - propanediols. Moreover the 2-amino - 1-(4-hydrocarbonylmercaptophenyl)-1,3-propanediols are utilizable as intermediates in the production of the 2 - amino - 1 - (4-hydrocarbonylsulfonylphenyl)-1,3-propanediols as hereinafter set forth:

In accordance with the invention, the new 2-aliphatic carboxylic acylamino - 1-(4-hydrocarbonylmercaptophenyl)-1,3-propanediols are obtained by the following process. An alpha-(aliphatic carboxylic acylamino) - 4 - hydrocarbonylmercaptoacetophenone (II) is treated with formaldehyde in the presence of sodium bicarbonate or equivalent alkaline condensation catalyst, thereby producing an alpha-(aliphatic carboxylic acylamino)-beta-hydroxy-4-hydrocarbonylmercaptoacetoxyphenone (III); and the propiophenone derivative (III) thus obtained is reduced by treatment with an oxidizable aluminium alkoxide containing not more than four carbon atoms in each alkyl group, thereby yielding the desired 2-(aliphatic carboxylic acylamino) - 1 - (4-hydrocarbonylmercaptophenyl) - 1,3-propanediol (Ia). The reactions involved in our process are represented by the following equations:



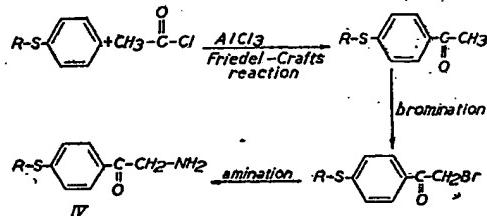
In the initial, or hydroxymethylation, step of our process, formaldehyde in the form of a gas, aqueous or alcoholic solution or para-formaldehyde is interacted with the acylamino-phenone (II). This reaction is most conveniently carried out at 20—50° C., but temperatures considerably above and below this temperature range, for example in the range 10 0—70° C., also afford satisfactory results. The amount of catalyst employed is not critical, but for best results we prefer to employ the smallest amount of catalyst sufficient to bring about a reasonably rapid reaction. In general, about 15 0.01—0.10 mole of the catalyst is sufficient to afford satisfactory results.

The latter, or reduction, step of our process can be carried out by treating the propiophenone derivative (III) obtained by the hydroxymethylation step with an oxidizable aluminium alkoxide containing not more than four carbon atoms in each alkyl group. This reduction step is carried out in an organic solvent which advantageously is a secondary alkanol containing not more than four carbon atoms. For purposes of convenience, we prefer to employ an alkanol corresponding to the alkoxide. The reduction can be carried out by heating the reaction mixture at 20—100° C. for several hours or until the reaction is completed. When an alkanol solvent is employed, we generally boil the reaction mixture while providing for slow distillation of the carbonyl compound, i.e. aldehyde or ketone, which is formed by oxidation of the alkanol while the propiophenone derivative (III) is simultaneously reduced. We generally prefer to employ as the reducing agent aluminium isopropoxide in isopropanol or aluminium sec.-butoxide in sec.-butanol. While as little as one equivalent of the alkoxide can be employed in the reduction, we generally prefer to employ about 1.5—2.0 equivalents of the aluminium alkoxide per equivalent of the propiophenone derivative (III) in order to assure optimum yields of the reduction product (Ia).

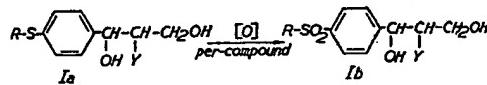
The alpha-(aliphatic carboxylic acylamino)-4-hydrocarbonylmercaptoacetophenones (II) employed as starting materials in our process are readily obtained, for example, by treating the appropriate alpha-amino-4-hydrocarbonylmercaptoacetophenones (IV) in conventional fashion with an aliphatic carboxylic acylating agent such as an acyl halide or anhydride. The acylation can be carried out, for example, by

heating the acylating agent and the amine (IV) in an anhydrous organic solvent or in an alkaline aqueous solution. The temperature of the reaction can be varied within rather wide limits, but a range of 0—100° C. is generally satisfactory.

The alpha-amino-4-(hydrocarbonylmercapto)acetophenones (IV) are themselves conveniently prepared from hydrocarbonyl phenyl sulfides in accordance with the following sequence of reactions:



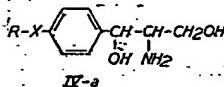
The new 2-aliphatic carboxylic acylamino-1-(4-hydrocarbonylsulfonylphenyl)-1,3-propanediols of the invention can in general be obtained by oxidizing a 2-aliphatic carboxylic acylamino-1-(4-hydrocarbonylmercapto-phenyl)-1,3-propanediol by treating it with a per-compound under acidic conditions. The reaction involved in this process is represented by the following equation:



The term "per-compound" as employed with reference to this aspect of the invention designates hydrogen peroxide or a substance derived therefrom which contains at least two oxygen atoms linked together, i.e. a peroxy linkage, in accordance with the definition set forth in *Per-Acids and Their Salts*, by T. S. Price, p. 1 ff., Longmans-Green (1912). Per-compounds suitable for use in obtaining the compounds of the invention include, for example, Caro's acid (H₂SO₅), ammonium persulfate [(NH₄)₂S₂O₈], potassium persulfate, hydrogen peroxide, peracetic acid, perbenzoic acid, perphthalic acid, sodium perborate and sodium percarbonate. Generally, it is preferable to employ as the oxidizing agent an organic peracid, such as peracetic acid or perbenzoic acid. Advantageously the oxidation is carried out in the presence of an organic solvent which is inert to the per-compound employed as the oxidant. The oxidation usually proceeds most satisfactorily at temperatures in the range 10—100° C., depending on the choice of oxidant, but for optimum yields, it is preferable, when using an organic per-acid, not to allow the reaction temperature to rise above about 65° C.

The 2-(aliphatic carboxylic acylamino)-1-(4-

hydrocarbonylmercapto- (or sulfonyl) phenyl)-1,3-propanediols (I) of our invention are readily deacylated by treatment with hot mineral acids to yield the corresponding free amines (IV-a), having the formula



- These novel amines (IVa) are readily acylated to yield acylamino derivatives and if desired can be readily reconverted to the aliphatic carboxylic acylamino derivatives (I). The amines (IVa) react with organic and inorganic acids to form salts. When compounds of our invention wherein the acylamino group is other than acetylarnino are desired, it is generally advantageous to prepare them by acylating the appropriate 2-amino-1-(4-hydrocarbonylmercaptophenyl)-1,3-propanediol which has been obtained by hydrolysis of the corresponding 2-acetylamino-1-(4-hydrocarbonylmercaptophenyl)-1,3-propanediol. It will be appreciated that this acylation of the aminodiol should be carried out under conditions which avoid the undesired acylation of the hydroxyl groups. Thus, the acylation should be carried out at temperatures below about 15° C. when an acid anhydride or acyl halide is employed as the acylating agent. When it is desired to dichloroacetylate the amides (IVa), it has been found convenient to employ as the dichloroacetylating agent an alkyl dichloroacetate, such as methyl dichloroacetate or ethyl dichloroacetate. Alternatively, the dichloroacetylating agent can be formed *in situ*. Thus, the amines (IVa) are treated with chloral cyanohydrin or, equivalently, with a chloral cyanohydrin-producing reaction mixture of chloral hydrate and an alkali metal cyanide, in the presence of an acid-binding agent. The acid-binding agent can be an inorganic base such as calcium carbonate, sodium carbonate, or magnesium oxide, or can be a tertiary organic amine such as triethylamine, pyridine, or butyldiethylamine. When chloral cyanohydrin itself is employed in the acylation, the reaction is preferably conducted at 10-20° C.; on the other hand, when a reaction mixture of chloral or chloral hydrate and an alkali metal cyanide is employed, it is preferable to conduct the reaction at a somewhat higher temperature, for example at 50-100° C. The following is illustrative of this modification of our process. Although, for example, good yields of 2-dichloroacetylamino-1-(4-methylmercaptophenyl)-1,3-propanediol are afforded by the route whereby alpha-amino-4-methylmercaptoacetophenone is dichloroacetylated, the acylation product is hydroxymethylated, and the hydroxymethylation product is reduced, it is economically advan-

tageous to dichloroacetylate 2-amino-1-(4-methylmercaptophenyl)-1,3-propanediol prepared by deacylation of 2-acetylamino-1-(4-methylmercaptophenyl)-1,3-propanediol.

It will be appreciated that in preparing the 2-(aliphatic carboxylic acylamino)-1-(4-hydrocarbonylmercaptophenyl)-1,3-propanediols (Ia) of our invention using racemic or optically inactive intermediates, the final products will of course be obtained in a racemic or optically inactive form. When it is desired to obtain the optically active forms of the acylaminodiois (Ia) of our invention, we have found that it is generally most convenient to acylate the appropriate optically active 2-amino-1-(4-hydrocarbonylmercaptophenyl)-1,3-propanediol (derived by resolution of the racemic aminodiol) by treatment with an aliphatic carboxylic acyl chloride, anhydride, or alkyl ester as set forth hereinabove and illustrated in the following examples.

It will also be appreciated that when a racemic or optically inactive form of the 2-(aliphatic carboxylic acylamino)-1-(4-hydrocarbonylmercaptophenyl)-1,3-propanediol (Ia) is employed as the starting material in the oxidation process, there will of course be obtained a racemic form of the 2-(aliphatic carboxylic acylamino)-1-(4-hydrocarbonylsulfonylphenyl)-1,3-propanediol (Ib). On the other hand, when an optically active form of the starting material (Ia) is employed in the process, the product (Ib) will likewise be optically active. The optically active forms of the starting material (Ia) are readily obtained as follows: A racemic form of the compound (Ia) is deacylated by treatment with a hot mineral acid to yield a racemic form of 2-amino-1-(4-hydrocarbonylmercaptophenyl)-1,3-propanediol which is resolved through use of an optically active organic acid. The optically active forms of the amines thus obtained are then treated with an aliphatic carboxylic acylating agent to yield the desired optically active forms of the compound (Ia).

The invention is illustrated by the following examples without, however, being limited thereto.

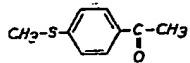
EXAMPLE 1.

A. ALPHA-AMINO-4-METHYLMERCAPOACETO-PHENONE HYDROCHLORIDE.

110 g. of thiophenol was added with stirring to a mixture of 90 ml. of 35% aqueous sodium hydroxide solution and 400 ml. of water in a 2-liter, 3-neck flask. To the resulting mixture, there was added 139 g. of dimethyl sulfate from a dropping funnel at such a rate that the temperature of the reaction mixture did not rise above 60° C. while applying external ice cooling to the reaction vessel. The addition of the dimethyl sulfate required about five to ten minutes. After the addition of dimethyl sulfate was completed, stirring of the reaction mixture was continued for about one hour,

and then the mixture was cooled. The thioanisole which separated from the mixture was dissolved in about 400 ml. of chloroform. The chloroform solution was separated, washed with 100 ml. of dilute aqueous sodium hydroxide solution, and dried over anhydrous calcium sulfate. (In other experiments, isolation of the product from the chloroform solution resulted in recovery of thioanisole in a yield of 90—95% of the theoretical based on the quantity of thiophenol employed).

The chloroform solution of thioanisole was filtered free from the calcium sulfate directly into a 2-liter, 3-neck flask fitted with a stirrer, thermometer, dropping funnel, and outlet tube (for escape of hydrogen chloride gas) protected by a drying tube. Sufficient anhydrous chloroform was added to the filtrate to bring the volume up to about 800 ml. and the solution was cooled by means of an ice-methanol bath. 165 g. of aluminium chloride was then added rapidly to the chloroform solution, while keeping the temperature of the solution below 10° C. 106 g. of acetyl chloride was added to the solution by means of a dropping funnel while still maintaining the temperature of the reaction mixture below 10° C. As the addition of the acetyl chloride proceeded, a yellow solid gradually separated from the mixture. (In some instances, it was found desirable to add an additional quantity of dry chloroform to the reaction mixture in order to facilitate stirring). When the addition of the acetyl chloride was completed, the cooling bath was removed and the reaction mixture was allowed to warm to 20° C. while continuing vigorous stirring. The thick reaction mixture was then decomposed by pouring it into a liter of ice and water containing 30—50 ml. of concentrated hydrochloric acid with vigorous stirring to ensure complete decomposition of the complex. The chloroform layer, which contained 4-methylmercaptoacetophenone, having the formula

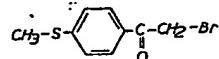


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was separated and employed directly in the subsequent step. (In other experiments, by evaporation of the chloroform solution there was obtained in 96—98% yield 4-methylmercaptoacetophenone in a high degree of purity).

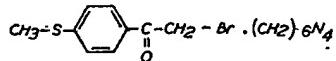
The chloroform solution of 4-methylmercaptoacetophenone was placed in a 3-liter, 3-neck flask fitted with a stirrer, a dropping funnel, and an outlet tube for escape of hydrogen bromide gas. The volume of the chloroform solution was brought up to about 1600 ml. by the addition of chloroform. About 40 g. of bromine was added to the solution and the mixture was allowed to stand until the

reaction was initiated, as evidenced by evolution of hydrogen bromide. Stirring of the mixture was then begun and a further quantity of 120 g. of bromine was added during a period of three to five minutes. The reaction mixture was then placed under reduced pressure by application of a water aspirator in order to remove the major portion of the hydrogen bromide. The temperature of the solution, which contained alpha-bromo-4-methylmercaptoacetophenone, having the formula



gradually fell, due to evaporation, to about 10—15° C. (A sample of this bromo ketone, isolated in another experiment, was obtained in the form of small white leaflets, which melted at 65.5—66.5° C., after recrystallization from methanol).

To the cold chloroform solution of alpha-bromo-mercaptoacetophenone, there was added 140 g. of hexamethylenetetramine. The temperature of the mixture rose gradually to about 30—35° C., and a white solid separated from the mixture. The mixture was stirred for about two hours and then the solid was collected on a filter and washed with chloroform. The product thus obtained consisted of alpha-bromo-4-methylmercaptoacetophenone-hexamethylenetetramine adduct, having the formula



and melting at approximately 140° C. with decomposition.

The alpha-bromo-4-methylmercaptoacetophenonehexamethylenetetramine adduct obtained in the preceding step was placed in a 3-liter flask with 750 ml. of ethanol and 375 ml. of concentrated hydrochloric acid. As the mixture was stirred, producing a slurry, the solid gradually went into solution. The reaction product subsequently began to separate from the solution. The reaction mixture was then cooled to 10° C., filtered, and the filter cake was washed with 100 ml. of cold ethanol. The damp filter cake was then slurried for a few minutes at 40—50° C. with 600 ml. of water containing 25 ml. of concentrated hydrochloric acid. After cooling the slurry to 5—10° C., the white solid was collected on a filter, washed with 100 ml. of water containing 5 ml. of concentrated hydrochloric acid, and dried. There was thus obtained 135—141 g. of alpha-amino-4-methylmercaptoacetophenone hydrochloride, having the formula

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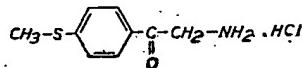
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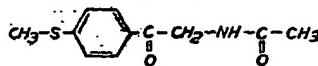
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A sample of this product when recrystallized from water formed large white leaflets which melted at 234.5—235° C. (dec.).

5 B. ALPHA-ACETYLAMINO-4-METHYLMERCAPTO-
 ACETOPHENONE.

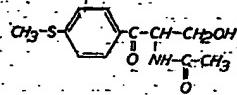
A slurry of 11 g. of alpha-amino-4-methylmercaptoacetophenone hydrochloride in 50 ml. of water containing 100 g. of ice was stirred 10 vigorously and to the slurry were added in one portion 10 ml. of acetic anhydride followed by a solution of 14.5 g. of sodium acetate trihydrate in 60 ml. of water. The temperature of the reaction mixture, which did not rise 15 during addition of the acetic anhydride and sodium acetate, was allowed to rise to room temperature (about 25° C.) and stirring was continued for an additional two hours. Sufficient concentrated hydrochloric acid was then 20 added to make the reaction mixture acid to Congo Red paper (to dissolve any unreacted aminoketone), and the white solid in the mixture was then collected on a filter. This solid was washed with 30 ml. of water and dried. 25 There was thus obtained 10 g. of alpha-acetylamino-4-methylmercaptoacetophenone, having the formula



30 which melted at 133.2—134.6° C. after recrystallization from acetone in the form of broad white needles.

C. ALPHA-ACETYLAMINO-BETA-HYDROXY-4-
 METHYLMERCAPTOPROIOPHENONE.

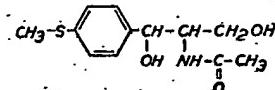
A mixture of 15 g. of alpha-acetylamino-4-35 methylmercaptoacetophenone, 70 ml. of ethanol, 25 ml. of water, 10 ml. of formalin (37% aqueous solution of formaldehyde), and a solution of 0.3 g. of sodium bicarbonate in 10 ml. of water was stirred at 35° C. for two 40 hours. The original thick slurry gradually thinned out and after about ten minutes the reaction mixture was a pale yellow solution. At the end of the two-hour period, the solution was refrigerated for about ten hours. The 45 crystalline solid which separated from the cooled solution was collected on a filter and washed with 20 ml. of water. There was thus obtained 10.5 g. of alpha-acetylamino-beta-hydroxy-4-methylmercaptopropiophenone, having the formula



This product was purified by recrystallization from ethyl acetate to yield white fluffy needles which melted at 125.6—127.8° C.

D. 2-ACETYLAMINO-1-(4-METHYLMERCAPTO-
 PHENYL)-1,3-PROPANEDIOL. 55

A mixture of 5 g. of alpha-acetylamino-beta-hydroxy-4-methylmercaptopropiophenone, 20 g. of aluminium isopropoxide, and 120 ml. of isopropanol was slowly distilled through a fifteen-inch column until the distillate gave no test for acetone. This distillation required about seven hours. The excess isopropanol was then distilled from the reaction mixture and the residue was heated for thirty minutes from a solution of 10 g. of sodium chloride in 100 ml. of water. The resulting suspension was filtered while hot and the aluminium hydroxide residue thus collected was washed several times with ether. From the filtrate there separated a white solid in the form of tiny leaflets. This solid was collected on a filter and washed with 15 ml. of ether. There was thus obtained 1.5 g. of 2-acetylamino-1-(4-methylmercaptophenyl)-1,3-propanediol, having the formula

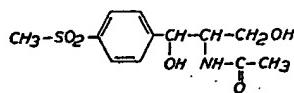


which melted at 167—168° C. Recrystallization from water and then nitroethane raised the melting point to 172.1—173.5° C. 80

E. 2-ACETYLAMINO-1-(4-METHYLSULFONYL-
 PHENYL)-1,3-PROPANEDIOL.

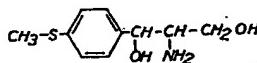
1.95 g. of a 2-acetylamino-1-(4-methylmercaptophenyl)-1,3-propanediol was slurried in 20 ml. of acetone and to the slurry was added dropwise 4.5 ml. of 40% peracetic acid. (The term "40% peracetic acid" is employed in this and the succeeding examples to designate a commercial preparation of peracetic acid consisting of an aqueous solution containing approximately 40% peracetic acid, 5% of hydrogen peroxide, 39% of acetic acid, and 1% of sulfuric acid, the percentages being by weight). The temperature of the reaction mixture was maintained at 46° C. or below by ice-cooling of the reaction vessel. After the addition of the peracetic acid was completed, stirring of the reaction mixture was continued for two hours, after which time the mixture was cooled to 5° C. The white solid which separated was collected on a filter and washed with two 5 ml. portions of cold acetone. This product was recrystallized from nitroethane to yield 1.02 g. of 2-acetylamino-1-(4-methylsulfonylphenyl)-1,3-propanediol in the form of white leaflets 100 105

which melted at 172.7—173.7° C., and having the formula:



EXAMPLE 2.

- 5 A. 2-AMINO-1-(4-METHYL MERCAPTO PHENYL)-1,3-PROPANEDIOL.
- A mixture of 50 parts by weight of racemic 2-acetyl amino - 1 - (4-methyl mercaptophenyl) - 1,3-propanediol obtained as described above in Example 1, 100 parts by weight of concentrated hydrochloric acid, and 500 parts by weight of water was warmed on a steam bath for thirty minutes. The resulting solution was cooled to about 40° C. and was then made strongly alkaline by addition of 35% aqueous sodium hydroxide solution. The alkaline solution was then refrigerated. The white solid which separated from the cooled solution was collected on a filter. There was thus obtained 27 parts by weight of 2-amino-1-(4-methyl mercaptophenyl) - 1,3-propanediol, having the formula



This product melted at 130.7—131.9° C. after recrystallization from methanol.

- 25 A solution of 17.5 g. of the 2-amino-1-(4-methyl mercaptophenyl) - 1,3 - propanediol described above, which of course was a racemic or optically inactive form of the compound, in 100 ml. of methanol and a solution of 13 g. of d-tartaric acid in 100 ml. of methanol were mixed and the mixture was allowed to stand at 15—20° C. for about six hours. The solid which had separated from the solution during this period was then collected on a filter, the methanolic filtrate being retained for treatment as described below. There was thus obtained 18 g. of solid which melted at 190—196° C. This solid was suspended in 150 ml. of water and sufficient dilute hydrochloric acid was added to effect solution of the solid. To the solution thus obtained there was added 50 ml. of 35% aqueous sodium hydroxide solution which caused the separation of 11.7 g. of yellowish solid from solution. This solid melted at 127—135° C. Two recrystallizations of this product from methanol yielded 1.5 g. of coarse white needles which melted at 152—153° C. This product was a levo-rotary form of 2-amino-1 - (4-methyl mercaptophenyl) - 1,3-propanediol having $[\alpha]_D^{25} = -21^\circ$ (1% solution in 95% ethanol).

The methanolic filtrate retained above was distilled on the steam bath to remove the methanol. The residue thus obtained was dis-

solved in 50 ml. of water and the resulting solution was treated with 15 ml. of 35% caustic solution. This caused the separation of 3.0 g. of white solid which melted at 141—150° C. This product was recrystallized twice from methanol, thus yielding 1.0 g. of white crystals consisting of a dextro-rotatory form of 2-amino - 1 - (4-methyl mercaptophenyl) - 1,3-propanediol which melted at 152—153° C. and had $[\alpha]_D^{25} = +21^\circ$ (1% solution in 95% ethanol).

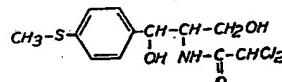
The racemic amine was also resolved in the following manner: 33.0 g. of racemic 2-amino-1-(4-methyl mercaptophenyl) - 1,3-propanediol and 34.6 g. of d-N-benzoyl threonine (m.p. 149—151° C.; obtained by benzoylation of d-threonine) were dissolved in 500 ml. of methanol by warming. Crystallization was initiated by cooling the solution to 25° C. and scratching the inner walls of the container. The solution was refrigerated at 5° C. for about ten hours and then the crystals which had separated from solution were collected on a filter, the filtrate (A) being retained for recovery of the dextro-rotatory amine as described below. The solid on the filter was washed with a few ml. of cold methanol and dried at 70° C. There was thus obtained 31.3 g. of levo-rotary 2-amino-1-(4-methyl mercaptophenyl) - 1,3-propanediol d-N-benzoyl threonine salt which melted at 184—186° C. This crop of salt was dissolved in 100 ml. of water containing 6.2 ml. of concentrated hydrochloric acid and the solution was then made alkaline by addition of 13 ml. of 35% aqueous sodium hydroxide solution. 20 g. of sodium chloride was dissolved in this solution which was then cooled to 5° C. A heavy crop of crystals separated from the solution and this solid was collected on a filter, washed with a little saturated aqueous sodium chloride solution and dried at 70° C. There was thus obtained 15.0 g. of crude levo-rotary 2-amino-1 - (4-methyl mercaptophenyl) - 1,3-propanediol which melted at 147—150° C. This product was recrystallized from 150 ml. of methanol to yield 11.9 g. of the pure levo-rotary amine which melted at 151—153° C. By concentrating the mother liquor, 3.0 g. of solid consisting largely of the racemic amine was recovered.

The filtrate (A) retained as indicated above was evaporated at reduced pressure. The residue thus obtained was dissolved in 100 ml. of water containing 62 ml. of concentrated hydrochloric acid and the solution was made alkaline by addition of 13 ml. of 35% aqueous sodium hydroxide solution. 20 g. of sodium chloride was dissolved in this solution which was then cooled to 5° C. The heavy crop of crystalline solid which separated from the solution was collected on a filter, washed with a few ml. of saturated aqueous sodium chloride solution and dried at 70° C. There was thus obtained 13.5 g. of crude dextro-rotatory 2-amino-1-(4-

5 methylmercaptophenyl)-1,3-propanediol. This product was recrystallized from methanol to yield 8.5 g. of the pure dextro-rotary amine which melted at 151-153° C. By concentrating the mother liquor, 5.0 g. of solid consisting largely of the racemic amine was recovered.

B. 2-DICHLOROACETYLAMINO - 1 - (4-METHYL-MERCAPTOPHENYL)-1,3-PROPANEDIOL.

10 A mixture of 1.1 g. of levo-rotary 2-amino-
1-(4-methylmercaptophenyl)-1,3-propanediol,
obtained as described above in part A, and 1.6
ml. of ethyl dichloroacetate was heated on a
steam bath for three hours. The resulting
viscous yellow oil was dissolved in 25 ml. of
15 ethylene chloride and filtered hot with char-
coal, and the filtrate was allowed to cool to
about 25° C. From the filtrate there separated
0.92 g. of tiny white leaflets which were col-
lected on a filter. Recrystallization of this pro-
duct, which was a dextro-rotary form of 2-di-
chloroacetyl amino - 1 - (4 - methylmercapto-
phenyl)-1,3-propanediol, having the formula



from nitroethane yielded the pure product, which melted at 111.6-112.6° C. and had $[a]_D^{25} = +12^\circ$ (1% solution in 95% ethanol).

In similar fashion, the dextro-rotary 2-amino-1-(4-methylmercaptophenyl)-1,3-propanediol was acylated with ethyl dichloroacetate to yield a levo-rotatory form of 2-dichloroacetyl amino-1-(4-methylmercaptophenyl)-1,3-propanediol, which melted at 111.6-112.6°C. and had $[\alpha]_D^{25} = -12^\circ$ (1% solution in 95% ethanol).

Also, in analogous fashion, the dichloroacetylation of the racemic amine with ethyl dichloroacetate yielded a racemic 2-dichloroacetyl-amino-1-(4-methylmercaptophenyl)-1,3-propanediol, m.p. 101.2-102.4° C.

40 Alternatively, the dichloroacetylation of the amines is carried out in the following manner. 6.4 g. of levo-rotary 2-amino-1-(4-methyl-mercaptophenyl)-1,3-propanediol obtained as described above in part A is dissolved in 60 ml.

45 of hot dioxane and the solution thus obtained is cooled to 20° C. To this solution is added 7.0 g. of chloral cyanohydrin followed by 6.3 g. of triethylamine, the latter reagent being added dropwise slowly while stirring the reac-

50 added dropwise slowly while stirring the reaction mixture and with sufficient cooling to maintain the reaction mixture at 10–20° C. After addition of the triethylamine is completed, the reaction mixture is stirred for a

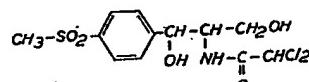
55 further period of several hours and then conveniently is allowed to stand overnight at room temperature (about sixteen hours at about 25° C.). The reaction mixture is then poured into 75 g. of ice water and concentrated hydro-

chloric acid is added in sufficient quantity to make the solution slightly acid to Congo Red. The acidified solution is refrigerated overnight, and the solid product which separates from solution is collected on a filter. There is thus obtained dextro-rotary 2-dichloroacetyl amino-1-(4-methylmercaptophenyl)-1,3-propanediol, m.p. 111.6-112.6°C., which is identical with the product obtained by treating the levo-rotary amine with ethyl dichloroacetate as described above. By substitution of the dextro-rotary and racemic 2-amino-1-(4-methyl-mercaptophenyl)-1,3-propanediols for the levo-rotary amine in this procedure, there are obtained, respectively, the levo-rotary and the racemic 2-dichloroacetyl amino-1-(4-methyl-mercaptophenyl)-1,3-propanediols, which are identical with the corresponding products of the dichloroacetylation procedure employing ethyl dichloroacetate.

C. 2-DICHLOROACETYLAMINO - 1-(4 - METHYL-SULFONYLPHENYL)-1,3-PROPANEDIOL.

7 g. of the levo-rotary 2-dichloroacetyl-amino-1-(4-methylmercaptophenyl)-1,3-propanediol obtained as described in part B above was dissolved in 30 ml. of acetone. To this solution there was added dropwise with stirring 10 ml. of 40% peracetic acid. The temperature during the reaction was maintained at 39-45° C. by cooling the reaction vessel. After stirring the mixture for two hours, it was diluted with 100 ml. of water and the solution allowed to stand over the weekend in the refrigerator. The solid which separated from the solution was collected on a filter, washed several times with ice water, and dried overnight at 70° C. There was thus obtained 6.2 g. of a levo-rotary 2-dichloroacetylamino-1-(4-methylsulfonylphenyl)-1,3-propanediol which melted at 164.3-166.3° C. and had $[\alpha]^{25} = -12^\circ$ (1% solution in 95% ethanol).

A dextro-rotatory 2-dichloroacetylamino-1-(4-methylsulfonylphenyl)-1,3-propanediol was prepared in similar fashion by oxidation of the dextro-rotatory 2-dichloroacetylamino-1-(4-methylmercaptophenyl)-1,3-propanediol obtained as described in part B above. This product melted at 165.2–166.6°C. and had $[\alpha]_D^{25} +13^\circ$ (1% solution in 95% ethanol), and had the formula:

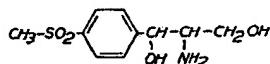


**D. 2-AMINO - 1-(4-METHYLSULFONYLPHENYL)
1,3-PROPANEDIOL.**

A mixture of 5 g. of the dextro-rotary 2-di-chloroacetyl-amino - 1 - (4 - methylsulfonyl-phenyl)-1,3-propanediol obtained as described above in part C, 9 ml. of concentrated hydrochloric acid, and 40 ml. of water was heated on a steam bath for one hour. The water was

removed from the resulting solution by distillation *in vacuo* to give a light yellow residual syrup which solidified on standing at room temperature (*circa* 25° C.) for several days.

5 This solid was heated to 60—70° C. with 20 ml. of saturated aqueous sodium chloride solution until all dissolved. The resulting solution was treated with 3.5 ml. of 35% aqueous sodium hydroxide solution and extracted while still warm with approximately 100 ml. of n-butanol. On cooling and standing, 0.9 g. of white crystals separated from the butanol extract. This product, which was levo-rotary 2-amino - 1 - (4-methylsulfonylphenyl) - 1,3-propanediol, having the formula



20 melted at 141.4—142.6° C. and had $[\alpha]_D^{25} = -19.8^\circ$ (1% solution in 95% ethanol). This water-soluble base formed a water-soluble hydrochloride which melted at 200.4—202.6° C. and had $[\alpha]_D^{25} = -26.0^\circ$ (1% solution in 95% alcohol).

25 In analogous fashion, when the levo-rotatory and the racemic 2-dichloroacetylaminoo-1-(4-methylsulfonylphenyl) - 1,3 - propanediols are deacylated by treatment with concentrated hydrochloric acid, there are obtained the dextro-rotatory and the racemic 2-amino-1-(4-methylsulfonylphenyl) - 1,3 - propanediols, respectively.

E. 2-DICHLOROACETYLAMINO - 1-(4-METHYL-SULFONYLPHENYL)-1,3-PROPANEDIOL.

30 Dichloroacetylation of the levo-rotatory, dextro-rotatory, and racemic 2-amino - 1-(4-methylsulfonylphenyl) - 1,3 - propanediols (obtained as described above in part D) by treatment with ethyl dichloroacetate or with chloralcyanohydrin in the presence of an acid-binding agent, or with a mixture of chloral hydrate, and alkali metal cyanide, and an acid-binding agent such as triethylamine, calcium carbonate, sodium carbonate, or pyridine, yields respectively the dextro-rotatory, levo-rotatory, and racemic 2-dichloroacetylaminoo-1-(4-methylsulfonylphenyl) - 1,3 - propanediols. These products obtained by acylation are identical with the respective acylamino products described above in part C obtained by the oxidation process.

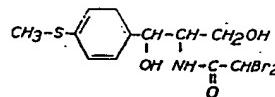
EXAMPLE 3.

A. 2-DIBROMOACETYLAMINO-1-(4-METHYL-MERCAPTOPHENYL)-1,3-PROPANEDIOL.

35 By refluxing the racemic 2 - amino - 1 - (4-methylmercaptophenyl) - 1,3-propanediol described above in part A of Example 2 with methyl dibromoacetate for about one hour using anhydrous ethanol as a reaction solvent, there is produced a racemic 2-dibromoacetyl-

amino-1-(4-methylmercaptophenyl) - 1,3-propanediol, having the formula

60



In analogous fashion, the dibromoacetylation of the levo-rotatory 2-amino - 1 - (4-methylmercaptophenyl)-1,3-propanediol described in Example 2A yields a dextro-rotatory form of the 2-dibromoacetylaminoo-1-(4-methylmercaptophenyl)-1,3-propanediol, and the enantiomeric dextro-rotatory aminodiol yields a levo-rotatory 2-dibromoacetylaminoo-1 - (4-methylmercaptophenyl)-1,3-propanediol.

65

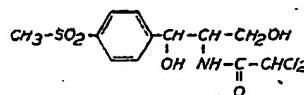
B. 2-DIBROMOACETYLAMINO-1-(4-METHYL-SULFONYLPHENYL)-1,3-PROPANEDIOL.

Oxidation of the racemic, dextro-rotatory, and levo-rotatory forms of 2-dibromoacetylaminoo-1-(4-methylmercaptophenyl) - 1,3 - propanediol obtained as described above in part A yields, respectively, racemic, dextro-rotatory, and levo-rotatory forms of 2-dibromoacetylaminoo-1 - (4-methylsulfonylphenyl)-1,3-propanediol.

70

EXAMPLE 4.

2-DICHLOROACETYLAMINO-1-(4-METHYL-SULFONYLPHENYL)-1,3-PROPANEDIOL.



A. ALPHA-DICHLOROACETYLAMINO - 4-METHYL-MERCAPTOACETOPHENONE.

85

217.7 g. of alpha-amino-4-methylmercaptopacetophenone hydrochloride obtained as described in part A of Example 1 was mixed with 4.5 liters of anhydrous benzene at 27° C. 166 g. of dichloroacetyl chloride was added in one portion to the mixture, and the resulting mixture was refluxed and stirred for fifteen to eighteen hours. After this period most of the solid had gone into solution. The reaction mixture was filtered hot through a preheated funnel and the filtrate was allowed to cool. The solid which separated from solution was collected on a filter, washed with benzene, and dried. There was thus obtained 230 g. of alpha-dichloroacetylaminoo - 4-methylmercaptopacetophenone having the formula

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95

100

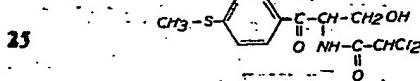
$\text{CH}_3-\text{S}-\text{C}_6\text{H}_4-\text{C}(=\text{O})-\text{CH}_2-\text{NH-C(=O)-CHCl}_2$

Recrystallization of this product from acetone yielded white needles which melted at 151.7—152.9° C.

105

B. ALPHA-DICHLOROACETYLAMINO-BETA-HYDROXY-4-METHYL MERCAPTOPROPIOPHENONE

292.2 g. of alpha-dichloroacetylaminobeta-hydroxy-4-methylmercaptoacetophenone was slurried with 14.5 liters of ethanol at 40° C. 15 g. of sodium bicarbonate and 150 ml. of formalin (37% aqueous solution of formaldehyde) were added to the mixture and stirring was continued while maintaining the temperature of the solution at 40—50° C. until all of the alpha-dichloroacetylaminobeta-4-mercaptopropiophenone had gone into solution. This required about eight hours. The suspended sodium bicarbonate was then removed by filtration and the volume of the filtrate was reduced to 2—2.5 liters by evaporation of ethanol from the solution under reduced pressure. The residual solution, which had an orange color, was refrigerated for about ten hours. The solid which separated from the solution was collected on a filter. There was thus obtained 232 g. of alpha-dichloroacetylaminobeta-hydroxy-4-methylmercaptoacetophenone having the formula

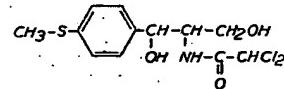


Recrystallization of this product from ethylene chloride yielded tiny white leaflets which melted at 147.7—148.5° C.

C. 2 - DICHLOROACETYLAMINO-1-(4-METHYL-MERCAPTOPHENYL)-1,3-PROPANEDIOL.

30 322.2 g. of alpha-dichloroacetylaminobeta-hydroxy-4-methylmercaptoacetophenone, 420 g. of aluminium isopropoxide, and three liters of anhydrous isopropanol were placed in a 5-liter flask and the mixture was heated at such a rate that distillation of liquid through a 15-inch column occurred at the rate of one drop per three to five seconds. Distillation was continued for sixteen to eighteen hours after which time a test for acetone in the distillate was negative. (The test for acetone was carried out using a 0.1% solution of 2,4-dinitrophenylhydrazine in accordance with the procedure described in Organic Reactions, Vol. II, page 200). The isopropanol remaining in the reaction mixture was removed by evaporation at reduced pressure. The dark red viscous residue thus obtained was heated on a steam bath for about forty-five minutes with 2.5 liters of water containing 200 g. of sodium chloride. The sodium chloride was added to reduce the tendency of aluminium hydroxide to form a gel. The hot suspension was filtered to remove aluminium hydroxide. The collected aluminium hydroxide was slurried several times with ether to remove the adhering red oil and the ether extracts were combined with the filtrate. The combined ether solutions were dried over anhydrous calcium sulfate and the ether was

removed from the dry solution by distillation. There was thus obtained 310—320 g. of a dark red viscous oil. This oil was dissolved in 1600 ml. of ethylene dichloride, filtered with charcoal, and the filtrate was cooled. The solid which separated from the filtrate consisted of 180—195 g. of 2-dichloroacetylaminobeta-hydroxy-4-methylmercaptoacetophenone having the formula

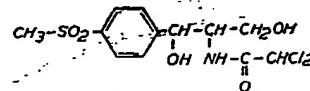


which melted at 98—100° C. This product was purified by recrystallization from 550 ml. of nitroethane followed by an additional recrystallization from ethylene chloride. There was thus obtained 125 g. of the pure product which melted at 101.2—102.4° C.

In another experiment, the reduction step was carried out in the following manner. A mixture of 9.6 g. of alpha-dichloroacetylaminobeta-hydroxy-4-methylmercaptoacetophenone, 6.5 g. of aluminium isopropoxide, and 90 ml. of anhydrous isopropanol was refluxed for about thirty-five minutes with provision for slow distillation of acetone and isopropanol from the solution. The remaining solvent was then removed by evaporation at reduced pressure. The residue thus obtained yielded 5.8 g. of 2-dichloroacetylaminobeta-hydroxy-4-methylmercaptoacetophenone having the formula

D. 2 - DICHLOROACETYLAMINO - 1-(4-METHYL-SULFONYLPHENYL)-1,3-PROPANEDIOL.

21 ml. of 40% peracetic acid was added to a stirred solution of 15.0 g. of 2-dichloroacetylaminobeta-hydroxy-4-methylmercaptoacetophenone dissolved in 55 ml. of acetone. External cooling of the reaction vessel with ice was applied and the rate of addition of peracetic acid was adjusted so that the temperature of the reaction mixture did not rise above 40° C. The reaction mixture was then stirred one hour and was cooled to —5° C. The solid which separated from solution was collected on a filter. There was thus obtained 14.0 g. of a white solid consisting of 2-dichloroacetylaminobeta-hydroxy-4-methylmercaptoacetophenone having the formula:

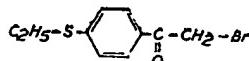


EXAMPLE 5.

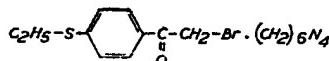
A. ALPHA-AMINO-4-ETHYL MERCAPTOACETO-PHENONE HYDROCHLORIDE.

337 g. of diethyl sulfate was added from a dropping funnel to a stirred solution of 200 g.

of thiophenol in 800 ml. of 10% aqueous sodium hydroxide. The reaction mixture was then stirred for two hours. During this period the temperature of the mixture gradually rose to 65° C. and then decreased to room temperature (about 25° C.) and the desired reaction product, ethyl phenyl sulfide, separated from the mixture as an oil. This oil was extracted from the mixture with 800 ml. of chloroform. The chloroform solution of ethyl phenyl sulfide thus obtained was dried for several hours over anhydrous calcium sulfate. The dry solution was then placed in a 3-liter, 3-neck flask fitted with a stirrer, thermometer, and drying tube. The solution was stirred and cooled to -10°C. and 175 ml. of acetyl chloride was added. 300 g. of anhydrous aluminum chloride was then added portionwise while keeping the temperature of the reaction mixture at 5-15° C. After the addition of the aluminum chloride was completed, the reaction mixture was allowed to warm to 20° C. and was poured into about 2 kg. of ice. The chloroform layer, which contained the desired 4-ethylmercaptoacetophenone, was separated from the mixture and placed in a 5-liter, 3-neck flask fitted with a stirrer and dropping funnel. To the stirred solution there was added 75 g. of bromine. After the reaction was initiated, as shown by the evolution of hydrogen bromide, an additional 225 g. of bromine was added as rapidly as was practical. The hydrogen bromide evolved from the mixture was removed by applying reduced pressure to the stirred solution, which contained alpha-bromo-4-ethylmercaptoacetophenone, having the formula

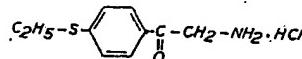


(A sample of the bromoketone isolated in another experiment melted at 74.4-75.4° C. after recrystallization from petroleum ether followed by recrystallization from methanol). To the residue thus obtained, there was added 256 g. of hexamethylenetetramine, and the mixture was stirred for two hours. The solid yellowish alpha-bromo-4-ethylmercaptoacetophenone-hexamethylenetetramine adduct having the formula



was collected on a filter, washed with chloroform and sucked partially dry on the filter. The adduct was mixed with 760 ml. of concentrated hydrochloric acid and 1540 ml. of ethanol, and the mixture was stirred for about six hours. The resulting suspension was cooled to 5° C., and was filtered and washed with

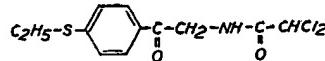
about 200 ml. of ethanol. The solid was then slurried with one liter of warm water containing 20 ml. of concentrated hydrochloric acid. This suspension was cooled to 5° C. and then filtered. The collected solid was washed with about 300 ml. of ice water and dried. There was thus obtained 211 g. of alpha-amino-4-ethylmercaptoacetophenone hydrochloride, having the formula



This product melted at 186.5° C. (dec.) after recrystallization from water which had been made slightly acid with dilute hydrochloric acid.

B. ALPHA-DICHLOROACETYLAMINO-4-ETHYL-MERCAPTOACETOPHENONE.

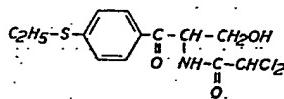
A mixture of 200 g. of alpha-amino-4-ethylmercaptoacetophenone hydrochloride and 4.5 liters of benzene was placed in a 12-liter, 3-neck flask fitted with a stirrer and a reflux condenser with water trap. The benzene was distilled slowly until no more water collected in the water trap. 147 g. of dichloroacetyl chloride was added to the mixture in a single portion and the resulting mixture was refluxed for fifteen hours. The evolution of hydrogen chloride had practically ceased at the end of this period and all of the solid in the mixture had dissolved. The hot solution was filtered. On cooling, there separated from the filtrate 139 g. of white solid which consisted of alpha-dichloroacetylamino-4-ethylmercaptoacetophenone having the formula



This product melted at 127.6-128.8° C. after recrystallization from ethylene chloride. An additional 66 g. of the product was recovered by evaporation of the filtrate to a volume of 600 ml., cooling, and collecting the solid which separated from solution.

C. ALPHA - DICHLOROACETYLAMINO - BETA-HYDROXY-4-ETHYL MERCAPTOPROPIONOPHENONE.

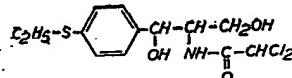
A mixture of 200 g. of alpha-dichloroacetylamino-4-ethylmercaptoacetophenone, 100 ml. of formalin (37% aqueous solution of formaldehyde), 1600 ml. of ethanol, and 10 g. of sodium bicarbonate was stirred at 40-50° C. for ten hours. The mixture was allowed to stand at room temperature for about fifteen hours and was then cooled to 10° C. The solid which separated from the cooled solution was collected on a filter, was washed with 150 ml. of ethanol, and dried. There was thus obtained 204 g. of alpha-dichloroacetylamino-beta-hydroxy-4-ethylmercaptopropionophenone, having the formula



which melted at 150—152° C. When recrystallized in the form of small white leaflets from ethylene chloride, the pure compound melted at 153.2—154.3° C.

D. 2-DICHLOROACETYLAMINO-1-(4-ETHYL-MERCAPTOPHENYL)-1,3-PROPANEDIOL.

A mixture of 140 g. of alpha-dichloroacetyl-amino - beta - hydroxy-4-ethylmercapto propiophenone, 400 g. of aluminium isopropoxide, and 1500 ml. of isopropanol was distilled slowly for fifteen hours. The excess isopropanol was removed by distillation at reduced pressure. Two liters of water containing 200 g. of sodium chloride was added to the red viscous residue and the mixture was heated about thirty minutes on a steam bath. The hot mixture was filtered and the filter cake was washed thoroughly with several 200 ml. portions of ethyl ether. The dark red ether layer was separated from the filtrate, dried over anhydrous calcium sulfate, and the ether was removed by evaporation. There was thus obtained as a residue 128 g. of red oil. This oil was taken up in 400 ml. of benzene and the hot solution was filtered with charcoal. On cooling the filtrate 84 g. of white solid separated from the solution. Recrystallization of this product from 300 ml. of ethylene chloride yielded 73 g. of pure 2-dichloroacetylamino - 1 - (4 - ethylmercapto-phenyl)-1,3-propanediol, having the formula

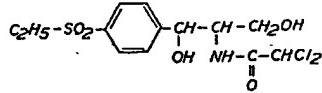


which melted at 92.4—93.4° C.

E. 2-DICHLOROACETYLAMINO-1-(4-ETHYL-SULFONYLPHENYL)-1,3-PROPANEDIOL.

22 ml. of 40% peracetic acid was added dropwise to a stirred solution of 18.5 g. of 2-dichloroacetylamino - 1 - (4 - ethylmercapto-phenyl)-1,3-propanediol dissolved in 50 ml. of acetone. External cooling of the reaction vessel with ice was applied and the rate of addition of peracetic acid was adjusted so that the temperature of the reaction mixture did not rise above 40° C. After completion of the addition of peracetic acid, the reaction mixture was stirred for one hour and was then cooled to —5° C. The solid which separated from solution was collected on a filter and washed with two portions each of 20 ml. of cold acetone. There was thus obtained 17.5 g. of 2-dichloroacetylamino - 1 - (4 - ethylsulfonylphenyl)-1,3-propanediol in the form of a white solid which

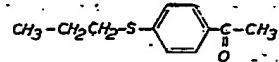
melted at 184.0—185.0° C., and had the formula:



EXAMPLE 6.

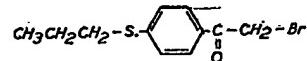
A. ALPHA-AMINO-4-n-PROPYLMERCAPTOACETO-PHENONE HYDROCHLORIDE.

A suspension of 226 g. of aluminium chloride in one liter of dry chloroform was placed in a 3-liter, 3-neck flask fitted with a stirrer, drying tube, dropping funnel, and thermometer. The suspension was stirred and cooled to 5° C. with stirring and 145 g. of acetyl chloride was added. 235.5 g. of n-propyl phenyl sulfide was then added dropwise at 5° C. The reaction mixture was stirred for fifteen minutes after addition of the sulfide was completed, and was then poured into 1.5 kg. of ice containing 25 ml. of concentrated hydrochloric acid. The chloroform layer was separated from the mixture and the chloroform was removed from the solution by distillation. The residual oil was fractionally distilled, and the fraction boiling at 207° C. at 45—48 mm. of mercury was collected. There was thus obtained 253 g. of colorless oil which solidified upon standing. This product, which was 4-n-propylmercaptoacetophenone, having the formula



melted at 37.7—39.1° C.

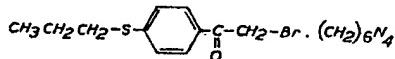
208 g. of bromine was added to a solution of 254 g. of 4-n-propylmercaptoacetophenone in 2 litres of chloroform. After five or ten minutes, the evolution of hydrogen bromide from the reaction mixture had practically ceased, and the mixture was washed with 2 liters of 5% aqueous sodium bicarbonate solution containing ice. The chloroform layer was separated from the mixture and the chloroform was removed from the chloroform solution by distillation at reduced pressure. There was thus obtained as a residue 300 g. of alpha-bromo-4-n-propylmercaptoacetophenone having the formula



in the form of an orange colored oil which was used directly in the next step of the process. Crystallization of a sample of this product from petroleum ether yielded a white solid which melted at approximately 43° C.

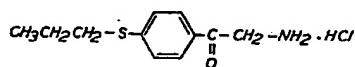
95 g. of hexamethylenetetramine was added with stirring to a solution of 176 g. of alpha-

- 5 bromo - 4-n-propylmercaptoacetophenone dissolved in 850 ml. of acetonitrile. The temperature of the reaction mixture rose from 28° C. to 42° C. and a pale yellow solid separated from solution. After stirring the mixture for two hours, the solid was collected on a filter, washed with two 150 ml. portions of acetonitrile, and with 300 ml. of water, and dried. There was thus obtained, as a pale yellow solid,
- 10 174 g. of alpha-bromo-4-n-propylmercaptoacetophenone-hexamethylenetetramine adduct having the formula



15 which melted at approximately 135° C. with decomposition.

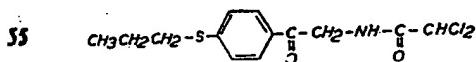
20 92 g. of alpha-bromo-4-n-propylmercaptoacetophenone-hexamethylenetetramine adduct was mixed with a solution of 90 ml. of concentrated hydrochloric acid and 225 ml. of methanol, and the mixture was stirred and refluxed for thirty minutes. Initially, the mixture became dark red in color and after about ten minutes ammonium chloride separated from the solution. The ammonium chloride was removed by filtration, and the filtrate was cooled to -5° C. The solid which separated from the cooled solution was collected on a filter and dissolved in 125 ml. of hot water. The aqueous solution was cooled to 0° C. and the solid which separated from solution was collected on a filter. There was thus obtained 27 g. of alpha-amino-4-n-propylmercaptoacetophenone hydrochloride having the formula



35 which melted at approximately 155° C. with decomposition.

B. ALPHA-DICHLOROACETYLAMINO-4-n-PROPYLMERCAPTOACETOYPHENONE.

40 27 g. of alpha-amino-4-n-propylmercaptoacetophenone hydrochloride was added to 500 ml. of benzene and the resulting mixture was refluxed until no more water distilled off into a water separator. 41 g. of dichloroacetyl chloride was then added and the mixture was stirred and refluxed for thirty minutes. During this period all of the ketoamine dissolved. The resulting reaction mixture was concentrated under reduced pressure, and the residue thus obtained was refrigerated. The solid which separated from the cooled solution was collected on a filter, washed with 5 ml. of benzene, and dried. There was thus obtained 16.5 g. of alpha-dichloroacetylamino-4-n-propylmercaptoacetophenone, having the formula



which was recrystallized from benzene as a white solid which melted at 123.2-123.8° C.

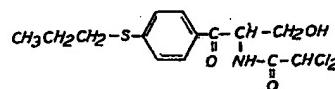
C. ALPHA - DICHLOROACETYLAMINO - BETA-HYDROXY - 4 - n-PROPYLMERCAPTOPROPIONPHENONE.

60

A mixture of 13 g. of alpha-dichloroacetyl-amino-4-n-propylmercaptoacetophenone, 100 ml. of ethanol, and 8 ml. of formalin (37% aqueous solution of formaldehyde) containing 0.8 g. of sodium bicarbonate dissolved therein was stirred at 40-43° C. for four hours. The reaction mixture was then cooled and the solid which separated from the solution was collected on a filter. There was thus obtained 12.5 g. of alpha-dichloroacetyl-amino-beta-hydroxy - 4-n - propylmercapto-propiophenone, having the formula

65

70



This product was recrystallized from ethylene chloride, thereby yielding 10 g. of the pure compound which melted at 133.4-136.8° C.

75

D. 2-DICHLOROACETYLAMINO - 1-(4-N-PROPYLMERCAPTOPHENYL)-1,3-PROPANEDIOL.

80

A mixture of 9 g. of alpha-dichloroacetyl-amino-beta-hydroxy - 4 - n-propylmercapto-propiophenone, 20 g. of aluminium isopropoxide, and 200 ml. of dry isopropanol was distilled slowly for three hours. The isopropanol remaining in the reaction mixture was removed by distillation at reduced pressure. The resulting brown pasty residue was warmed with 200 ml. of saturated aqueous sodium chloride solution, and then filtered. The residual aluminium hydroxide on the filter was washed with several portions of ether. The ether layer was separated from the filtrate and dried over anhydrous calcium sulfate. The ether was then removed from the ether solution by evaporation at reduced pressure. The dark amber oil obtained as a residue was taken up in 100 ml. of hot benzene, filtered with charcoal, and the filtrate was diluted with petroleum ether just short of permanent turbidity. On standing, there separated from the solution 4 g. of solid which was recrystallized from benzene and then from ethylene chloride. The product thus obtained, which was 2-dichloroacetyl-amino - 1-(4-n-propylmercaptophenyl) - 1,3-propanediol, having the formula

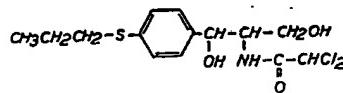
85

90

95

100

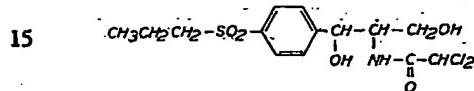
105



melted at 91.8-94.8° C.

E. 2-DICHLOROACETYLAMINO - 1-(4-n-PROPYL-SULFONYLPHENYL) - 1,3-PROPANEDIOL.

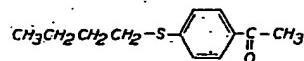
2 g. of 2-dichloroacetylamino - 1 - (4-n-propylmercaptophenyl) - 1,3-propanediol was dissolved in 6 ml. of acetone and to this solution there was added 2 ml. of 40% peracetic acid with cooling. After stirring the reaction mixture for about one and one-half hours, the solid which separated from solution was collected on a filter. This product, which was 2-dichloroacetylamino - 1 - (4-n-propylsulfonylphenyl)-1,3-propanediol, weighed 1.2 g. and melted at 182.9-184.5° C. and had the formula:



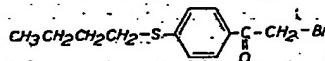
EXAMPLE 7.

A. ALPHA-AMINO-4-n-BUTYL MERCAPTOACETOPHENONE.

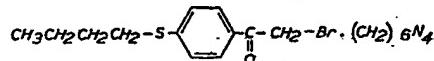
This compound was prepared in a manner analogous to that described in part A of Example 6 above for the preparation of the corresponding n-propylmercapto compound. 250 g. of n-butyl phenyl sulfide was treated with 133 g. of acetyl chloride in the presence of 220 g. of aluminium chloride. There was thus obtained 206 g. of 4-n-butylmercaptoacetophenone, having the formula



which boiled at 138-140° C. at 0.8 mm. and melted at 24-25° C. after crystallization from petroleum ether at 0° C. 110 g. of 4-n-butylmercaptoacetophenone dissolved in one liter of chloroform was treated with 80 g. of bromine to yield 168 g. of alpha-bromo-4-n-butylmercaptoacetophenone, having the formula



This compound was recrystallized from petroleum ether, thus yielding large colorless crystals which melted at approximately 63° C. 60 g. of alpha-bromo-4-n-butylmercaptoacetophenone dissolved in 300 ml. of acetone-nitrile was treated with 30 g. of hexamethylene tetramine, thereby producing 88 g. of alpha-bromo - 4 - n - butylmercaptoacetophenone-hexamethylene tetramine adduct, having the formula



which melted at approximately 113° C. with decomposition.

A mixture of 86 g. of alpha-bromo-4-n-butylmercaptoacetophenone - hexamethylene tetramine adduct, 85 ml. of concentrated hydrochloric acid, and 170 ml. of ethanol was stirred for about ten hours. The ammonium chloride which separated from the mixture as a white solid was removed by filtration and discarded. The filtrate, after partial evaporation at room temperature under reduced pressure, yielded 13.5 g. of a pale yellowish solid which melted at 140-145° C. (dec.). The filtrate from collection of this solid was reduced in volume by evaporation and a further yield of 35 g. of the product was obtained as a brown gummy solid. This gummy solid was suspended in 50 ml. of acetone, the solution was cooled in an ice-methanol bath, the solid which separated from the cooled solution was collected on a filter and washed several times with cold acetone. There was thus obtained 26.5 g. of a yellowish-tan solid which melted at 140-145° C. (dec.). The two crops of product melting at 140-145° C. were combined and the 40 g. of product was recrystallized from 100 ml. of water containing 3 ml. of concentrated hydrochloric acid. There was thus obtained 32.5 g. of alpha-amino - 4 - n - butylmercaptoacetophenone hydrochloride having the formula



in the form of white flaky crystals. A sample of this product was recrystallized from ethanol and then again from water acidulated with hydrochloric acid to yield the pure compound which melted at 175.5-179.3° C. (dec.).

B. ALPHA-DICHLOROACETYLAMINO-4-n-BUTYL MERCAPTOACETOPHENONE.

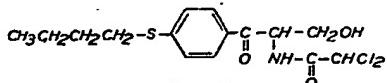
A mixture of 27 g. of dry alpha-amino-4-n-butyl - mercaptoacetophenone hydrochloride, 125 ml. of anhydrous benzene, and 15 ml. of dichloroacetyl chloride was stirred and heated for fifteen minutes on a steam bath. The reaction mixture was then cooled and the solid which separated from solution was collected on a filter. There was thus obtained 31.6 g. of alpha-dichloroacetylamino - 4-n-butylmercaptoacetophenone having the formula



Recrystallization of this product from benzene yielded fluffy white needles which melted at 127.4-128° C. with sintering at 120.2° C.

C. ALPHA - DICHLOROACETYLAMINO - BETA-HYDROXY - 4 - n - BUTYL MERCAPTOPROPIOPHENONE.

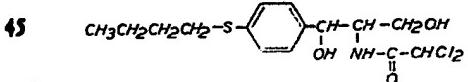
A mixture of 47.5 g. of alpha - dichloroacetylamino - 4 - n - butylmercaptoacetophenone, 300 ml. of ethanol, and 2 g. of sodium bicarbonate dissolved in 23 ml. of formalin (37% aqueous solution of formaldehyde) was heated at 40-45° C. for four hours. The slurry was cooled to 10° C., filtered, and the solid residue was washed with 40 ml. of methanol and dried. There was thus obtained 41 g. of alpha - dichloroacetylamino - beta-hydroxy - 4 - n - butylmercaptopropiophenone having the formula



which when recrystallized from benzene in the form of small white crystals, melted at 123.0-123.8° C.

D. 2- DICHLOROACETYLAMINO-1-(4-n-BUTYL-MERCAPTOPHENYL)-1,3-PROPANEDIOL.

35 g. of alpha - dichloroacetylamino - beta-hydroxy-4-n-butylmercaptopropiophenone, 65 g. of aluminium isopropoxide, and one liter of dry isopropanol were distilled slowly for fifteen hours. The excess isopropanol was removed from the reaction mixture by evaporation under reduced pressure, and the reddish residue thus obtained was heated for thirty minutes with 400 ml. of water containing 40 g. of sodium chloride. The aluminium hydroxide which separated from solution was removed by filtration and the filter cake was washed thoroughly with ether. The reddish ether layer was separated from the filtrate, dried over anhydrous calcium sulfate, and the ether was removed from the ether solution by evaporation under reduced pressure. The light red viscous oily residue thus obtained was taken up in 120 ml. of benzene, filtered with charcoal, and the filtrate was cooled. From the filtrate there separated 14 g. of 2-dichloroacetylamino - 1-(4 - n - butylmercaptophenyl)-1,3-propanediol, having the formula

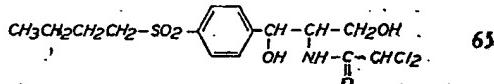


which was recrystallized from benzene and then from ethylene chloride to yield a white waxy solid which melted at 85.5-87.0° C.

E. 2-DICHLOROACETYLAMINO - 1-(4-n-BUTYL-SULFONYLPHENYL) - 1,3-PROPANEDIOL.

3.5 g. of 2-dichloroacetylamino - 1 - (4-n-butylmercaptophenyl) - 1,3 - propanediol was dissolved in 10 ml. of acetone and to this solution there was added with cooling 4 ml. of

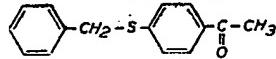
40% peracetic acid. After stirring the reaction mixture for one hour, it was cooled to -10° C. The solid which separated from the solution was collected on a filter. There was thus obtained 2.5 g. of 2-dichloroacetylamino - 1-(4-n-butylsulfonylphenyl)-1,3-propanediol in the form of a pure white solid which melted at 131.6-132.8° C. An additional 1.0 g. of this product was obtained by evaporation of the filtrate. The product had the formula:



EXAMPLE 8.

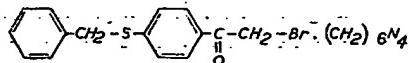
A. ALPHA-AMINO - 4-BENZYL MERCAPTOACETO-PHENONE HYDROCHLORIDE.

340 g. of benzyl phenyl sulfide was dissolved in 1200 ml. of anhydrous chloroform and 120 ml. of acetyl chloride was added to the solution. The resulting mixture was cooled to -10° C. and 226 g. of aluminium chloride was added portionwise at such a rate that the temperature of the reaction mixture did not exceed 0° C. After the addition of the aluminium chloride was completed, the mixture was stirred and allowed to warm to 21° C. The mixture was then poured into ice water. The red chloroform layer was separated from the aqueous layer, washed with 300 ml. of dilute hydrochloric acid, and dried over anhydrous calcium sulfate. The chloroform was then evaporated from the chloroform solution. There was thus obtained as a residue 402 g. of a dark red oil. This oil was dissolved in 1200 ml. of petroleum ether and the resulting solution was filtered hot with charcoal. The yellow filtrate was cooled in an ice bath. 154 g. of yellow solid separated from the cooled solution. This product was recrystallized twice from ethanol and once from petroleum ether. There was thus obtained, in the form of fine white needles which melted at 113.9-115.3° C., 4-benzylmercaptoacetophenone, having the formula



95 g. of 4-benzylmercaptoacetophenone was dissolved in one liter of chloroform and was treated with 62.5 g. of bromine by a procedure similar to the bromination described above in Example 1A. To the solution of alpha-bromo-4-benzylmercaptoacetophenone thus obtained there was added 56 g. of hexamethylenetetraamine and the mixture was stirred for two hours. The pinkish-white solid which separated was collected on a filter and washed with 200 ml. of chloroform. The resulting crude alpha-

bromo-4-benzylmercaptoacetophenone - hexamethylenetetramine adduct, having the formula



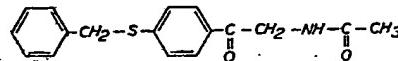
- 5 was hydrolyzed directly by stirring it for about ten hours at room temperature (about 25° C.) with 180 ml. of concentrated hydrochloride and 360 ml. of ethanol. The reaction mixture was then cooled to 10° C. The solid was collected on a filter and dried. There was thus obtained 145 g. of crude reaction product. Ammonium chloride was removed from this product by slurring it with 400 ml. of hot water for ten minutes and then cooling the solution to 10° C. 67 g. of solid separated from the cooled solution. This product was further purified by recrystallization from water containing a little hydrochloric acid. There was thus obtained alpha-amino-4-benzylmercaptoacetophenone hydrochloride, having the formula



in the form of white leaflets which melted at 214.5-216.5° C. (dec.).

25 B. ALPHA-ACETYLAMINO-4-BENZYLMERCAPTOACETOPHENONE.

To a slurry of 52 g. of alpha-amino-4-benzylmercaptoacetophenone hydrochloride, 250 ml. of water and 500 g. of ice there was added 40 ml. of acetic anhydride followed by the immediate addition of a solution of 60 g. of sodium acetate trihydrate in 250 ml. of water. The reaction mixture was stirred and allowed to warm to room temperature (about 25° C.), and was then made acid to Congo by addition of hydrochloric acid. The solid was separated from the mixture by filtration, washed with water, and dried. A small sample of this product was purified by recrystallization from acetone. There was thus obtained alpha-acetylamino-4-benzylmercaptoacetophenone, having the formula

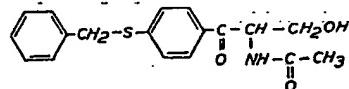


45 in the form of white needles which melted at 162.6-163.8° C.

C. ALPHA-ACETYLAMINO-BETA-HYDROXY-4-BENZYLMERCAPTOPROIOPHENONE.

The crude product from part B was slurried and warmed at 40° C. with 3.5 liters of ethanol. To this mixture were added 45 ml. of formalin (37% aqueous solution of formaldehyde) and 4 g. of sodium bicarbonate.

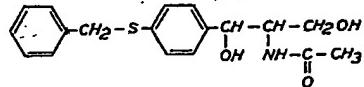
Stirring of the reaction mixture at 40° C. was continued for twenty-four hours. The suspended sodium bicarbonate was removed from the solution by filtration and the filtrate was evaporated to a volume of about 100 ml., diluted with water, and the white solid which separated from solution was collected on a filter. There was thus obtained 49 g. of pale yellow solid. This product was recrystallized once from ethylene chloride, and once from nitroethane. There was thus obtained alpha-acetylamino-beta-hydroxy-4-benzylmercapto-*propiophenone*, having the formula



which melted at approximately 161° C.

D. 2-ACETYLAMINO-1-(4-BENZYLMERCAPTOPHENYL)-1,3-PROPANEDIOL.

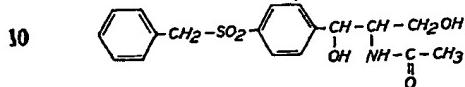
A mixture of 23 g. of alpha-acetylamino-beta-hydroxy-4-benzylmercapto-*propiophenone*, 30 g. of aluminium isopropoxide, and one liter of dry isopropanol was refluxed for eighteen hours. During this time isopropanol and acetone were allowed to distil slowly from the reaction mixture. The remaining isopropanol was then distilled off under reduced pressure and the dark red residue was heated for thirty minutes with about 200 ml. of 5% aqueous sodium chloride solution on a steam bath. The mixture was filtered and the residue thus collected was heated with 200 ml. of ethylene chloride. The mixture was filtered hot to remove aluminium hydroxide, and the filtrate was cooled. 11 g. of solid separated from the cooled filtrate. This solid was collected and purified by recrystallization, first from nitroethane, then from isopropanol, and finally, again from nitroethane. There was thus obtained, in the form of white leaflets which melted at 157.0-158.0° C., 2-acetylamino-1-(4-benzylmercaptophenyl)-1,3-propanediol, having the formula



E. 2-ACETYLAMINO-1-(4-BENZYSULFONYL-PHENYL)-1,3-PROPANEDIOL.

To a slurry of 0.6 g. of 2-acetylamino-1-(4-benzylmercaptophenyl)-1,3-propanediol in 3 ml. of acetone there was added at 20° C. 2 ml. of 40% peracetic acid in one portion. The temperature of the mixture rose to 55° C. and the solution became clear followed almost immediately by the separation of a solid product. The mixture was stirred for an addi-

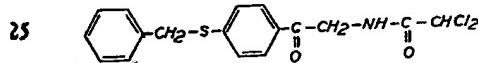
tional thirty minutes and then cooled to 10° C. The solid product was collected on a filter and washed with three 2 ml. portions of acetone. There was thus obtained 0.6 g. of white solid. Recrystallization of this solid from 70 ml. of nitroethane yielded small white leaflets of 2-acetylaminoo - 1 - (4-benzylsulfonylphenyl) - 1,3-propanediol which melted at 222.9-223.9° C. and had the formula:



EXAMPLE 9.

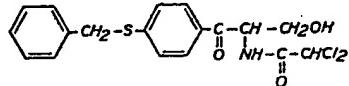
A. 2 - DICHLOROACETYLAMINO - 1-(4-BENZYL-MERCAPTOPHENYL)-1,3-PROPANEDIOL.

15 12 g. of alpha - amino - 4-benzylmercaptoacetophenone hydrochloride (obtained as described above in part A of Example 8), 8 g. of dichloroacetyl chloride, and 500 ml. of dry benzene were refluxed for seven hours. The hot solution was then filtered, 5 g. of solid residue was collected on the filter and the benzene filtrate on cooling yielded an additional 8 g. of the same product, which was alpha - dichloroacetylaminoo - 4 - benzylmercaptoacetophenone, having the formula



This product, when purified by crystallization, first from ethylene chloride and then from nitroethane, melted at 185.6-186.4° C.

30 Proceeding in the manner set forth in the above examples, hydroxymethylation of the alpha - dichloroacetylaminoo - 4 - benzylmercaptoacetophenone by treatment with formaldehyde in the presence of an alkaline condensation catalyst yields alpha-dichloroacetylaminoo - beta - hydroxy - 4 - benzylmercapto-
35 propiophenone, having the formula



40 Reduction of this compound with aluminium isopropoxide in isopropanol yields 2-dichloroacetylaminoo - 1 - (4 - benzylmercaptophenyl) - 1,3-propanediol.

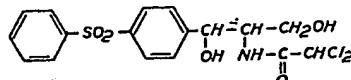
B. 2 - DICHLOROACETYLAMINO - 1-(4-BENZYL-SULFONYLPHENYL)-1,3-PROPANEDIOL.

45 When, for the 2-acetylaminoo - 1-(4-benzylmercaptophenyl)-1,3-propanediol employed as a reactant in the oxidation procedure described in Example 8E, there is substituted 2-dichloroacetylaminoo - 1 - (4 - benzylmercapto-phenyl)-1,3-propanediol, there is obtained as

the product 2-dichloroacetylaminoo - 1 - (4 - benzylsulfonylphenyl)-1,3-propanediol.

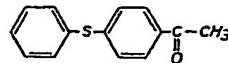
EXAMPLE 10.

2-DICHLOROACETYLAMINO-1-(4-PHENYL-SULFONYLPHENYL)-1,3-PROPANEDIOL.



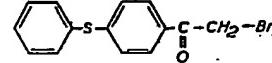
A. ALPHA-AMINO - 4-PHENYLMERCAPTOACETO-PHENONE HYDROCHLORIDE.

A mixture of 190 g. of diphenyl sulfide, 146 g. of aluminium chloride, and one liter of anhydrous chloroform was stirred and cooled to -5° C. 80 g. of acetyl chloride was added to the mixture slowly, the temperature of the mixture being kept at -5° C. to +5° C. When all of the acetylchloride had been added, stirring was continued for one hour while the reaction mixture was gradually allowed to warm to room temperature. The mixture was then poured into ice water. The chloroform layer was separated from the mixture and the chloroform was removed from the chloroform solution by distillation under reduced pressure. The residue thus obtained was dissolved in a hot mixture of 150 ml. of benzene and 150 ml. of petroleum ether. When the solution was cooled, 158 g. of 4-phenylmercaptoacetophenone, having the formula



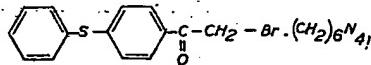
separated from solution. This product melted at approximately 66° C.

80 A solution of 53 g. of 4-phenylmercaptoacetophenone in 500 ml. of chloroform was treated with 36 g. of bromine at room temperature. After the bromination was completed, and excess hydrogen bromide was removed from the reaction mixture, a sufficient quantity of 5% aqueous sodium bicarbonate solution was added to render the mixture alkaline to litmus. The chloroform layer was separated and distilled under reduced pressure to remove the chloroform. There was thus obtained as an oil, 69 g. of crude alpha-bromo - 4-phenylmercaptoacetophenone, having the formula

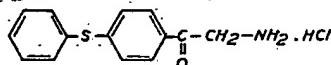


90 The 69 g. of oil was dissolved in 400 ml. of acetonitrile and 32.6 g. of hexamethylene-tetramine was added to the solution. The mixture was stirred for thirty minutes and the

white creamy solid was then collected on a filter. There was thus obtained 100 g. of crude alpha-bromo - 4-phenylmercaptoacetophenone-hexamethylenetetramine adduct, having the formula



which melted with decomposition at approximately 206° C. This product was stirred and heated on a steam bath for fifteen minutes with 250 ml. of ethanol and 120 ml. of concentrated hydrochloric acid. The ammonium chloride which separated from the mixture was removed by filtration and the filtrate was allowed to stand for several hours at room temperature. The white solid which separated from the solution was collected on a filter, dissolved in hot anhydrous ethanol, filtered hot with charcoal, and the filtrate was cooled. There separated from the cooled solution 22 g. of alpha-amino-4-phenylmercaptoaceto-phenone hydrochloride, having the formula



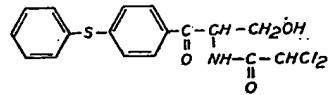
which melted at 216.7–217.0° C. (dec.).

B. ALPHA-DICHLOROACETYLAMINO - 4-PHENYL-MERCAPTOACETOPHENONE.

A mixture of 22 g. of alpha - amino - 4-phenylmercaptoacetophenone hydrochloride, 37 g. of dichloroacetyl chloride, and 150 ml. of dry benzene was heated under reflux for thirty minutes. The hot reaction mixture was then filtered. 12 g. of alpha - dichloroacetyl-amino - 4-phenylmercaptoacetophenone separated from the filtrate on cooling. This product melted at 138.5-139.7°C.

35 C. ALPHA - DICHLOROACETYLAMINO - BETA-HYDROXY - 4 - PHENYLMERCAPTOPROPIOPHENONE.

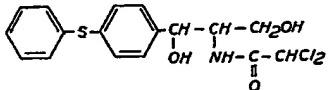
40 A mixture of 17 g. of alpha-dichloroacetyl-
amino - 4 - phenylmercaptoacetophenone, 125
ml. of ethanol, 10 ml. of formalin (37%
aqueous solution of formaldehyde), and 1 g.
of sodium bicarbonate was stirred and heated
at 40° C. for one hour and then allowed to
stand for several hours at room temperature
45 (about 25° C.). The reaction mixture was
then reheated to 40° C., filtered to remove
sodium bicarbonate, and the filtrate cooled.
11 g. of solid separated from the cooled
filtrate. This product was recrystallized from
50 ethylene chloride, thereby yielding 10.5 g. of
pure alpha-dichloroacetylamino-beta-hydroxy-
4-phenylmercaptoacetylphenone, having the
formula



which melted at 128.5—129.5° C.

D. 2-DICHLOROACETYLAMINO - 1 - (4 - PHENYL-MERCAPTOPHENYL)-1,3-PROPANEDIOL.

A mixture of 10 g. of alpha-dichloroacetyl-amino - beta-hydroxy-4-phenylmercaptopropiophenone, 20.4 g. of aluminium isopropoxide, and 100 ml. of dry isopropanol was distilled slowly for forty-five minutes. The excess isopropanol was then removed by distillation under reduced pressure and the residue was heated for thirty minutes with 100 ml. of 15% aqueous sodium chloride solution. The aluminium hydroxide which separated from the mixture was collected on a filter and washed thoroughly with ether. The aqueous filtrate was also extracted with ether, and the ether washings and extracts were combined and dried over anhydrous calcium sulfate. The ether was then distilled from the filtrate under reduced pressure. There was thus obtained as a residue 5.0 g. of 2 - dichloroacetylamino-1-(4-phenylmercaptophenyl) - 1;3-propanediol, having the general formula

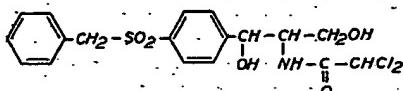


in the form of a red oil.

This was dissolved in about 40 ml. of ethylene dichloride, and the solution was treated with charcoal and then filtered. The filtrate was refrigerated for several hours and the solid product which separated from solution was recrystallized twice from ethylene dichloride. There was thus obtained 4 g. of 2-dichloroacetylamino - 1 - (4-phenylmercapto-phenyl)-1,3-propanediol which melted at 90.6 - 97.4° C.

E. 2-DICHLOROACETYLAMINO-1-(4-PHENYL-SULFONYLPHENYL)-1,3-PROPANEDIOL.

Oxidation of the 2-dichloroacetylamino-1-(4-phenylmercaptophenyl)-1,3-propanediol with peracetic acid in a manner similar to the oxidizing procedures described in the foregoing examples yields 2-dichloroacetylamino-1-(4-phenylsulfonylphenyl)-1,3-propanediol, having the formula



Thus, 12.7 g. of 2-dichloroacetylamino-1-(4-phenylmercaptophenyl)-1,3-propanediol was suspended in 125 ml. of water and to this suspension there was added 16.3 ml. of 40% peracetic acid. The solid product obtained by this reaction was crystallized twice from nitroethane with charcoaling. There was thus obtained 6.5 g. of 2-dichloroacetylamino-1-(4-phenylsulfonylphenyl)-1,3-propanediol, which melted at 124.9-127.3° C.

Proceeding in accordance with the teachings of the above examples there can be prepared the following compounds as well as the corresponding mercapto compounds:

15 2-Iodoacetylamino - 1 - [4-(*p*-tolylsulfonyl)phenyl]-1,3-propanediol, by oxidizing 2-iodoacetylamino-1-[4-(*p*-tolylmercapto)phenyl]-1,3-propanediol, which is prepared by hydroxymethylating alpha-iodoacetylamino-4-(*p*-tolylmercapto)-acetophenone and reducing the alpha-idoacetylamino-beta-hydroxy-4-(*p*-tolylmercapto)propiophenone thus obtained;

20 2-beta-chloropropionylamino - 1 - (4-cyclohexylsulfonylphenyl) - 1,3 - propanediol, by oxidizing 2-beta - chloropropionylamino-1-(4-cyclohexylmercaptophenyl) - 1,3 - propanediol, which is prepared by hydroxymethylating alpha-(beta-chloropropionylamino) - 4 - cyclohexylmercaptoacetophenone and reducing the alpha - (beta - chloropropionylamino) - beta-hydroxy - 4-cyclohexylmercaptoacetophenone thus obtained;

25 2-acetylaminio-1-(4-methallylsulfonylphenyl)-1,3-propanediol, by oxidizing 2-acetylaminio-1-(4-methallylmercaptophenyl)-1,3-propanediol, which is prepared by hydroxymethylating alpha - acetylaminio-4-methallylmercaptoacetophenone and reducing the alpha-acetylaminio-beta-hydroxy - 4 - methallylmercaptoacetophenone thus obtained;

30 2-trifluoroacetylamino - 1 - (4 - methallylsulfonylphenyl)-1,3-propanediol, by oxidizing 2-trifluoroacetylamino-1-(4-methallylmercaptophenyl)-1,3-propanediol, which is prepared by interacting ethyl trifluoroacetate and 2-amino-1-(4-methallylmercaptophenyl) - 1,3 - propanediol obtained by deacylating the corresponding 2-acetylaminio compound;

35 2 - (alpha - methylpropionylamino)-1-(4-isobutylsulfonylphenyl) - 1,3 - propanediol, by oxidizing 2 - (alpha-methylpropionylamino)-1-(4-isobutylmercaptophenyl) - 1,3 - propanediol, which is prepared by interacting 2-amino-1-(4-isobutylmercaptophenyl) - 1,3 - propanediol with alpha-methylpropionyl chloride; and
40 2-(alpha,beta-dichloropropionylamino)-1-(4-tert.-butylsulfonylphenyl)-1,3-propanediol, by oxidizing 2 - alpha,beta - dichloropropionylamino) - 1 - (4-tert.-butylmercaptophenyl)-1,3-

45 propanediol, which is prepared by hydroxymethylating alpha - (alpha,beta - dichloropropionylamino) - 4 - tert.-butylmercaptoacetophenone and reducing the alpha-(alpha,beta-dichloropropionylamino)-beta-hydroxy-4-tert-butylmercaptoacetophenone thus obtained.

The racemic and the dextro-rotary forms of the 2-aliphatic carboxylic acylamino - 1 - (4-hydrocarbonylsulfonylphenyl)-1,3-propanediols (I) of the invention have been found to have especially high antibiotic activity, being active against gram-negative and gram-positive bacteria and rickettsial organisms. In general, the dextro-rotary form is more active than the racemic form. In many instances, the dextro-rotary form has approximately twice the antibacterial activity of the racemic form.

What we claim is:—

1. A process for preparing threo acylamino diol compounds, which comprises reducing a compound of the formula III herein to produce a threo compound of the formula Ia herein.

2. A process according to claim 1, in which the compound of formula III is treated with an oxidizable aluminium alkoxide containing not more than four carbon atoms in each alkyl group.

3. A process according to claim 1 or 2, in which Y in the formulæ is haloalkanoylamino, e.g. dichloroacetylamino.

4. A process according to claim 1 or 2, in which alpha - dichloroacetylamino - beta-hydroxy - 4 - methylmercaptoacetophenone is treated with aluminium isopropoxide in isopropanol to produce threo 2-dichloroacetylamino - 1 - (4 - methylmercaptophenyl)-1,3-propanediol.

5. A process according to any one of the preceding claims, in which the compound of formula III is prepared by hydroxymethylating a compound of the formula II herein.

6. A process according to claim 5 in which the compound of formula II is treated with formaldehyde in the presence of a small amount of sodium bicarbonate.

7. A process for preparing threo acylamino diol compounds, which comprises acylating a threo compound of the formula IVa herein to produce a threo compound of the formula I herein.

8. A process according to claim 7, in which the acylating agent is a haloalkanoylating agent, e.g. a dichloroacetylating agent.

9. A process according to claim 7 or 8, in which R in the formulæ is alkyl, e.g. methyl.

10. A process according to claim 7 or 8, in which R in the formulæ is phenyl.

11. A process for preparing threo acylamino diol compounds, which comprises oxidizing a threo compound of the formula Ia herein to produce a threo compound of the formula Ib herein.

12. A process according to claim 11, in which the compound of formula Ia is treated with a per compound under acidic conditions.

13. A process according to claim 11 or 12, in which Y in the formulæ is haloalkanoylamino, e.g. dichloroacetylamino.

14. A process according to any one of claims 11-13, in which R in the formulæ is alkyl, e.g. methyl.

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15. A process according to any one of claims 11—13, in which R in the formulæ is aryl, e.g. phenyl.
16. A process according to any one of claims 5 11—15, in which the compound of formula Ia is treated with an organic per-acid, e.g. per-acetic acid.
17. The processes for preparing threo acyl-amino diol compounds of the formula I herein, substantially as set forth in the Examples.
- 10 18. Threo acylamino diol compounds of the formula I herein, whenever prepared by a process according to any one of the preceding claims.
- 15 19. A threo acylamino diol compound of the formula I herein.
20. A compound according to claim 19, in which Y in the formula is haloalkanoylamino, e.g. dichloroacetylarnino.
21. A compound according to claim 19 or 20, in which R in the formula is alkyl, e.g. methyl.
22. A compound according to claim 19 or 20, in which R in the formula is aryl, e.g. phenyl.

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Acylaminodiols and method for preparing same

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Applicant(s): STERLING DRUG INC

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Equivalents:

Abstract

The invention comprises threo-acylaminodiols of the general formula (wherein R represents a hydrocarbon radical of 1-7 carbon atoms, X represents S or SO₂, and Y represents an aliphatic carboxylic acylamino radical), and the manufacture thereof by: (a) acylating the corresponding free aminodiols (Y = NH₂); (b) (when X is S) reducing compounds of the general formula (preferably by means of an oxidizable aluminium alkoxide containing not more than 4 carbon atoms in each alkyl group); (c) (when X is SO₂) oxidizing the corresponding compounds in which X is S (preferably with a percompound under acidic conditions). The starting materials for processes (a) and (b) are obtainable by the processes of Specifications 746,015 and 746,016 respectively. The radical represented by R in the general formula may be benzyl, a cycloalkyl or alkenyl radical, or especially an alkyl or aryl radical, whilst that represented by Y may be, for example, alkanoylamino, nitroalkanoylamino, alkylmercaptoalkanoylamino, or especially haloalkanoylamino, and preferably contains 1-4 carbon atoms. The products, which may exist in racemic or in optically active forms, are useful as antibiotic agents, especially in their dextro-rotatory forms, or as intermediates therefor. In examples (in which all acylaminodiols and aminodiols are threo forms) (1) a - acetylamino-b - hydroxy-4 - methylmercaptopropiophenone is reduced with aluminium isopropoxide in isopropanol to 2 - acetylamino - 1 - (4 - methylmercaptophenyl)-1 : 3 - propanediol, which is oxidized with peracetic acid in acetone to the corresponding 4-methylsulphonyl compound; (2) 2-amino-1-(4-methylmercaptophenyl) - 1 : 3 - propanediol or either of its optically active isomers is dichloracetylated by heating with ethyl dichloracetate or by treatment with chloral cyanhydrin and triethylamine, and the products are oxidized as in (1) to the corresponding 2-dichloracetylaminio-1 - (4 - methylsulphonylphenyl) - 1 : 3 - propanediols; the same products are obtained by dichloracetylation of the corresponding 2 - amino-1 - (4 - methylsulphonylphenyl) - 1 : 3 - propanediols; chloral hydrate and an alkali metal cyanide may be used instead of chloral cyanhydrin, and calcium carbonate, sodium carbonate or pyridine instead of triethylamine. By analogous process are prepared: (3) 2-dibromacetylaminio - 1 - (4 - methylmercapto - and 4 - methylsulphonyl - phenyl) - 1 : 3 - propanediols; (4) the racemic products of (2) by the process of (1); (5)-(7), (9) and (10) racemic 2-dichloracetylaminio - 1 - (4 - ethyl - , - n propyl - , -n-butyl - , -benzyl - and -phenyl-mercapto-and - sulphonylphenyl) - 1 : 3 - propanediol; (8) racemic 2 - acetylaminio - 1 - (4 - benzylmercapto - and - sulphonyl - phenyl) - 1 : 3-propanediol. Further products and the corresponding starting materials and intermediates are listed in which R and Y have the following additional meanings: p-tolyl, cyclohexyl, methallyl, iso - and tert. - butyl; iodoacetylaminio, b - chloropropionylaminio, trifluoracetylaminio, a - methylpropionylaminio and a : b - dichloropropionylaminio. Still further radicals which may be represented by R and Y are: n-heptyl, isoamyl, allyl, cyclopentyl, o- and m-tolyl; mono- and di-bromacetylaminio, difluoracetylaminio, a - chloropropionylaminio, trichloracetylaminio, nitroacetylaminio, methyl-and ethylmercaptoacetylaminio, methylsulphonylacetylaminio, butyrylaminio, a : a - dichloropropionylaminio, cyanoacetylaminio, methoxyacetylaminio, acrylylaminio and a - hydroxypropionylaminio.

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